Clinical factors affecting pregnancy rates among infertile couples

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In a follow-up study of 1297 couples registered at a Nova Scotia infertility clinic with a complaint of infertility of at least 12 months' duration, the cumulative pregnancy rate at 36 months, with 95% confidence limits, was found to be 49 ± 4%. The predictors of pregnancy by univariate analysis were a favourable primary clinical diagnosis ($p < 0.001$), a duration of infertility of less than 3 years ($p < 0.001$), a single diagnosis for the infertility ($p < 0.001$), a previous pregnancy in the partnership ($p = 0.001$) and a length of marriage of less than 4 years ($p = 0.002$). Proportional hazards analysis confirmed these variables as predictors of pregnancy. The highest cumulative pregnancy rates after 12 and 36 months of follow-up were observed in cases of ovulation deficiency, and the lowest were seen in cases of tubal defects. However, before the process of diagnosing infertility begins, useful prognostic information can be determined from the length of marriage, the duration of infertility and the partnership's history of previous pregnancy.

Une étude catamnestique de 1297 couples stériles depuis au moins 12 mois inscrits à une clinique de stérilité de Nouvelle-Écosse a révélé un taux de grossesse cumulatif après 36 mois (avec un intervalle de confiance à 95%) de 49 ± 4%. Les facteurs prévisionnels de grossesse identifiés par une analyse de variance en plan simple ont été un diagnostic clinique primaire favorable ($p < 0.001$), une période de stérilité de moins de 3 ans ($p < 0.001$), un seul diagnostic relatif à la stérilité ($p < 0.001$), une grossesse antérieure au sein du couple ($p = 0.001$) et une durée du mariage de moins de 4 ans ($p = 0.002$). L'analyse des risques proportionnels a confirmé la valeur de ces variables comme facteurs prévisionnels de grossesse. Après 12 et 36 mois les plus forts taux cumulatifs de grossesse ont été observés pour les cas de déficit ovulatoire, et les plus faibles pour les cas de malformation tubaire. Toutefois, avant de procéder au diagnostic des causes d'une stérilité, des informations pronostiques utiles peuvent être obtenues à partir de la durée du mariage, de la durée de la stérilité et de l'histoire des grossesses antérieures du couple.

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Infertility is a disorder commonly seen by physicians in family practice and a number of medical specialties. In 1976 in the United States 10% of couples in which the wives were aged 15 to 44 years were found to be infertile;[1] if infertility is equally prevalent in Canada, then there are about 360 000 such couples here.[2] The management of infertility is influenced by the prognosis we can offer afflicted couples, but a bewildering variety of clinical and other conditions affect their pregnancy rates. The importance of these factors is not easily determined from the literature for two main reasons. First, the majority of reports are concerned with specific treatments or particular classes of infertile couples.[3] Second, the more general studies often fail to account for different periods of follow-up and for losses during follow-up.[4-6] As a result, the outcome for couples with infertility cannot be predicted accurately, and the choice of treatment or even adoption rests on inadequate information.

During a study of the clinical characteristics of infertile couples in Nova Scotia we analysed data on pregnancy rates; the results may be useful for counselling infertile couples. Our follow-up study made use of procedures collectively called survival analysis, which include life-table organization of the data, single-variable analysis with log-rank tests, and multiple-variable analysis using a proportional hazards model. Given appropriate data we could estimate the proportion of pregnancies, the time until pregnancy and the effect of additional factors on that time in couples with a particular history or disorder.

Methods

From Jan. 1975 to Aug. 31, 1980, 1375 couples registered at the Dalhousie University Infertility Centre in Halifax with the complaint of infertility. This clinic is a referral centre providing service to couples in Nova Scotia and to a small proportion of the infertile couples in New Brunswick and Prince Edward Island. Couples with infertility of less than 12 months' duration or with a history of failed pregnancy were excluded from the study. Also excluded were 78 couples in which the

woman was found to be pregnant at the first visit. The remaining 1297 couples were followed until they adopted a child, completed a pregnancy or became lost to follow-up. The period of observation for the findings in this report ended Aug. 31, 1982; the minimum period of follow-up for couples under observation was thus 2 years. Over the 7 years 257 couples (19.8%) were lost to follow-up.

Demographic and clinical data were obtained at the time of registration. After the initial history-taking and physical examination the diagnostic evaluation included determination of basal temperatures, endometrial biopsy, hysterosalpingography, postcoital testing and semen analysis; these were repeated as required. When the results of the initial pelvic examination or hysterosalpingography were abnormal, laparoscopy and the testing of tubal patency with methylene blue were carried out. Laparoscopy was also performed when pregnancy did not occur within the first year of observation.

Senior medical staff established the clinical diagnoses after the diagnostic investigation was completed. Women who had had amenorrhea for more than 3 months and those with a luteal-phase defect (endometrial maturation delayed 48 hours or more) or irregular menstrual cycles (intervals of more than 42 days) were considered to have an ovulation deficiency. The clinical diagnoses of tubal defect and endometriosis required laparoscopic confirmation. Seminal deficiency was defined as a sperm density of less than 20×10^6/mL or sperm motility of less than 40%, and the diagnosis required at least two semen analyses. Couples with no discoverable abnormalities after the conventional tests were classed as having idiopathic infertility. Treatment, when offered, included prescribed drugs, surgery and procedures such as artificial insemination. All pregnancies were confirmed by either delivery or pathology reports.

During the study, data on 107 clinical and demographic variables were recorded. The significance of relations among these variables was evaluated by means of the chi-square test. The mean time until pregnancy occurred (the interval from registration until the onset of the last menstrual period) among different groups of patients was analysed with the use of life tables, summarized in terms of 3-year pregnancy rates and compared for two or more groups by log-rank analysis.[7]

Table I—Characteristics of 1297 couples referred to Nova Scotia infertility clinic

Characteristic	No. (and %) of couples
Woman's age, yr	
20–24	315 (24)
25–29	611 (47)
30–34	314 (24)
> 34	57 (4)
Duration of infertility, mo	
12–23	445 (34)
24–35	334 (26)
36–47	179 (14)
48–71	177 (13)
> 71	162 (13)

Variables selected for p values of less than 0.1 were further evaluated by proportional hazards analysis with Cox's regression model.[8] In this procedure the data were examined to determine which combination of variables best predicted the time until the occurrence of pregnancy and to estimate the order of importance among them. The estimated regression coefficients describe the fitted regression model, and the ratio of each regression coefficient to its standard error, when squared, takes a χ^2 distribution with one degree of freedom.[9] For each covariable the exponential of the regression coefficient estimates the associated percentage change in the instantaneous pregnancy rate (the chance of pregnancy per unit time during the period of follow-up).

Results

The mean age (and standard error [SE]) of the women seen was 27.5 ± 0.1 years; infertility had persisted for a mean of 36.0 ± 0.8 months (Table I). There were 473 pregnancies among the 1297 couples registered, for a simple pregnancy rate of 36.5%. The rates of pregnancy loss were as follows: first-trimester abortion 12.5%, ectopic pregnancy 2.1%, and stillbirth or neonatal death 1.3%. The cumulative pregnancy rate at 36 months, with 95% confidence limits, adjusted for losses during follow-up, was 49.0 ± 4.1%.

The different primary clinical diagnoses gave the widest range of outcomes among all the variables examined (Fig. 1). Cumulative pregnancy rates at 36 months (with 95% confidence limits) were highest for couples with an ovulation disorder (65.8 ± 7.1%) and lowest for couples with a defect in tubal function (22.6

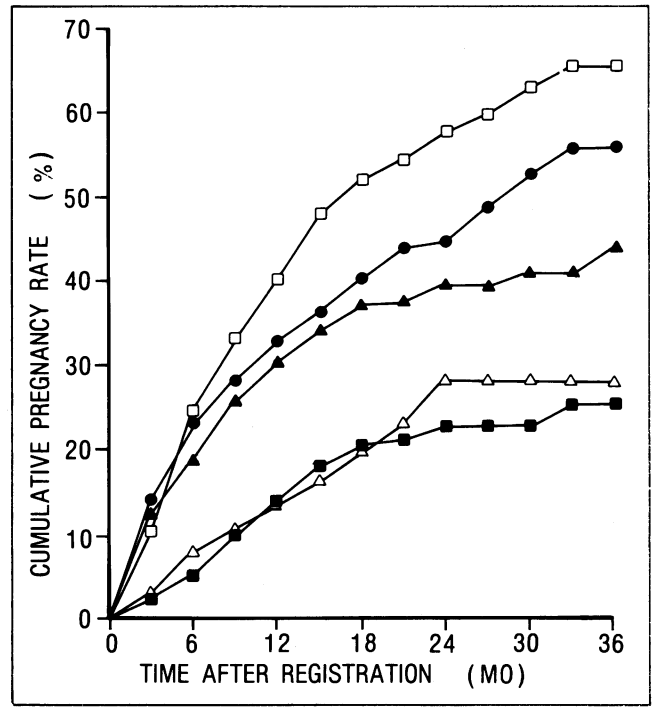

FIG. 1—Cumulative pregnancy rates among 1297 infertile couples grouped according to primary clinical diagnosis — ovulation deficiency (n = 383, □), idiopathic infertility (n = 265, ●), seminal deficiency (n = 387, ▲), endometriosis (n = 39, △) or tubal defect (n = 221, ■).

± 8.0%). The log-rank χ^2 value (with four degrees of freedom) was 63.6 ($p < 0.001$). Other findings strongly associated with a higher pregnancy rate were a duration of infertility of under 36 months, a single diagnosis for the infertility, a history of a previous pregnancy within the present partnership and a total length of marriage of less than 4 years (Table II). Variables that did not appear to be related to the likelihood of pregnancy were the age of the woman, a history of a previous pregnancy in another partnership, the place of residence, the coital frequency, the couple's social class, the wife's employment status, the husband's age and the year of registration. When more than one diagnosis for the infertility was found the nature of the additional diagnosis was not a predictor of pregnancy either.

We reanalysed the data using the proportional hazards model, which estimates the best combination of predictive variables. The ratio of the regression coefficients to the standard error expressed the strength of the association between each variable and the time until pregnancy occurred while accounting for the other variables with p values of less than 0.1 in the log-rank tests. For these variables the ratios were as follows: primary clinical diagnosis 6.65, number of diagnoses for the infertility 4.13, pregnancy history 3.65, duration of infertility 3.77 and length of marriage 2.21. The χ^2 value for the fitted model was 121.5 ($p < 0.001$).

Of the couples studied 52% received treatment, and the cumulative pregnancy rates at 36 months (with the SE) were 50 ± 4.6% for the treated couples and 46.2 ± 5.2% for the untreated couples. To account for possible differences arising from treatment, we stratified the data and repeated the proportional hazards analysis. The results of the stratified analysis did not differ from those obtained without stratification ($\chi^2 = 122.3$, $p < 0.001$), and the plotted log-minus-log survival functions for treated and untreated couples were parallel, which suggests that the hazard rates for the two groups were proportional. We then entered treatment into the model and found that the overall prediction was not improved ($\chi^2 = 121.8$). The coefficient:SE ratio for treatment as a variable was 0.88 ($p > 0.25$).

For each primary clinical diagnosis the cumulative pregnancy rates at 12 and 36 months are given in Table III by history of previous pregnancies and duration of infertility. The duration of infertility was not a predictor of pregnancy when there had already been a pregnancy in the partnership. Among all the categories tabulated, the couples with an ovulation deficiency had the best prognosis, and the couples with a tubal defect the worst.

The sample was not large enough to permit further subdivision of the groups according to the other predic-

Table III—Effect of pregnancy history, duration of infertility and primary clinical diagnosis on cumulative pregancy rates in the 1297 couples 12 and 36 months after registration

Couples; primary clinical diagnosis (no. of couples)	Cumulative pregnancy rate (%), with 95% confidence limits	
	12 mo	36 mo
With previous pregnancy in current partnership*		
Ovulation deficiency (85)	57 ± 11	80 ± 12
Idiopathic infertility (47)	46 ± 16	65 ± 19
Seminal deficiency (56)	39 ± 14	50 ± 15
Endometriosis (4)	–	–
Tubal defect (45)	8 ± 8	18 ± 14
With no previous pregnancy in current partnership and duration of infertility < 36 mo		
Ovulation deficiency (197)	42 ± 7	67 ± 9
Idiopathic infertility (131)	40 ± 9	62 ± 14
Seminal deficiency (184)	39 ± 8	52 ± 12
Endometriosis (18)	22 ± 19	38 ± 25
Tubal defect (94)	16 ± 8	28 ± 14
With no previous pregnancy in current partnership and duration of infertility ≥ 36 mo		
Ovulation deficiency (101)	21 ± 9	40 ± 13
Idiopathic infertility (89)	13 ± 8	40 ± 19
Seminal deficiency (147)	16 ± 6	31 ± 12
Endometriosis (17)	6 ± 11	20 ± 21
Tubal defect (82)	14 ± 8	25 ± 22

*The duration of infertility did not influence the cumulative pregnancy rates in this group.

Table II—Cumulative pregnancy rates 36 months after registration among the 1297 couples

Characteristic (no. of couples)	Cumulative pregnancy rate (%), with 95% confidence limits	Significance of differences between rates	
		Log-rank χ^2 value (df)	p value
Duration of infertility, mo			
< 36 (930)	55 ± 5	35.3 (1)	0.001
≥ 36 (367)	31 ± 6		
Causes of infertility			
< 2 (677)	54 ± 6	32.3 (1)	0.001
≥ 2 (620)	41 ± 6		
Pregnancy history			
Previous pregnancy in current partnership (220)	61 ± 10		
Pregnancy in previous partnership (152)	37 ± 10	13.0 (2)	0.001
No previous pregnancy (925)	48 ± 5		
Length of marriage, yr			
< 4 (667)	57 ± 6	9.97 (1)	0.002
≥ 4 (630)	39 ± 4		

tors (number of diagnoses for the infertility and length of marriage). However, we could calculate the relative magnitude of the instantaneous pregnancy rate from the regression coefficient. For marriages that had lasted more than 4 years (49% of those in our sample) the regression coefficient was -0.236, and e^{β} was 0.79, which indicated that the instantaneous pregnancy rate (the chance of pregnancy per unit time during the period of follow-up) was about 80% of that for couples married for less than 4 years. When there was more than one diagnosis for the couple's infertility (as in 48% of our sample) the coefficient β was -0.394, and e^{β} was 0.67, which meant that these couples had an instantaneous pregnancy rate about 70% of that for couples with a single diagnosis for the infertility.

Discussion

The primary clinical diagnosis, determined from clinical and laboratory findings, was the most significant predictor of pregnancy in the infertile couples referred to our centre. Other variables have been used to construct a table of cumulative pregnancy rates at 12 and 36 months (Table III) to assist in the management of infertile couples.

Some comparisons with the results of other infertility studies may give perspective to those reported here. Simple pregnancy rates ranging from 32% to 52% have been reported;[3-6,10-13] the rate in our series was 36.5%. Secondary infertility has been found in 36% to 43% of infertile couples,[5,6] compared with 29% of our series. The proportion of infertility assignable to each of several causes also varies widely: reported rates are 16% to 49% for ovulation deficiency, 9% to 24% for tubal defects, 13% to 30% for seminal deficiency, and 2% to 20% for idiopathic infertility.[3-5,11,14,15] We found endometriosis less frequently than other North American clinics;[11,16] our values were more like those of Europe and the Middle East.[3-6] The mean duration of infertility in our patients was 3.0 years, compared with reported figures of 2.9, 3.3 and 3.9 years.[3-5,10,11] If the duration of infertility is used as an estimate of severity, the composition of our sample appears to lie somewhere between that seen in primary care and that seen in metropolitan clinics with concentrated referral patterns. Treatment rates of 60% and 40% have been reported,[10,11] compared with 52% in our series.

Although the use of cumulative pregnancy rates to describe the outcome of infertility is not new,[11,17,18] a brief description of this application of life-table methods may be helpful. Also called survival or failure-time analysis, these methods are superior to the use of simple pregnancy rates, which do not account for losses during follow-up or differing lengths of follow-up. Life-table methods were developed for the analysis of outcomes in chronic diseases, such as cancer, and allow for differing periods of observation. These methods also depend on the assumption that the outcome for subjects no longer under observation (censored observations) is similar to the observed outcomes.[19] As life-table methods simply tabulate the occurrence of an event during the period that follows a well defined starting point, it is immaterial whether the event is a failure (such as death or a recurrence of disease) or a success (such as pregnancy).

In life-table analysis for infertility the date of registration is the starting point, and the date the patient is last seen is the censored time. For couples experiencing pregnancy the date of the last menstrual period is the terminal event. Computer programs produce a column of cumulative survivals (s[x]) for each interval (3 months in our study) during the period of follow-up.[20] The cumulative pregnancy rate is equal to $(1 - s[x])$. However, the cumulative pregnancy rate (with 95% confidence limits) should not be used directly for the comparison of results in different groups. Instead, a series of comparisons during each succeeding interval is summed, and the resulting log-rank estimator has a χ^2 distribution.[7] Multiple-variable analysis for life tables, which combines the theory of regression analysis with life-table theory, has been developed during the last decade.[8,9] Although the analysis is complex, the cumulative pregnancy rate is straightforward, and it summarizes the information in the life table in a clear and succinct manner.

Through proportional hazards analysis we selected five clinical characteristics that are predictors of pregnancy among infertile couples. Two of these, the primary clinical diagnosis and the number of diagnoses for the infertility, require the completion of a diagnostic process involving tests for deficiencies of ovulation and seminal function, and examinations for tubal defects or endometriosis, which can be identified only by laparoscop-

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ic examination. However, three other factors that account for some of the variability in the outcome can be assessed by asking three simple questions. These relate to the duration of infertility, the length of marriage and the pregnancy history. To illustrate, 307 of the couples in our study had been married more than 4 years, had been infertile for at least 3 years and had had no history of pregnancy in the partnership; their cumulative pregnancy rate (and SE) at 36 months, regardless of diagnosis, was 33 ± 4%. Another 58 couples had been married 4 years or less, had had less than 3 years of infertility and had given a history of pregnancy in their partnership; their cumulative pregnancy rate at 36 months was 80 ± 10%.

Infertile couples who are given some tentative reassurance based on this easily obtained information may be less inclined to undergo immediate diagnostic tests. Similar information about the prognosis may be helpful in counselling infertile couples about treatment and adoption.

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